REMARKS

With this amendment, claims 1 and 5-9 are pending in the present application. Claims 10-13 have been canceled without prejudice to subsequent revival. For convenience, the Examiner's rejections are addressed in the order in which they were presented in the November 2, 2001 Office Action. Reconsideration is respectfully requested.

THE INVENTION

The present invention provides a novel method of manufacturing IgG4 immune globulin free of IgG1, IgG2 and IgG3 subtypes for the treatment of diseases and conditions, including serious insect sting allergies. Recently, it has been recognized that IgG4 content is increased in persons exposed to certain allergens. Advantageously, the present application provides a method of preparing IgG4, essentially free from other IgG subtypes, for injection into allergic individuals. IgG4 pure preparations contain less protein and more blocking antibody per unit weight, thereby conferring immunity in patients while reducing risks of aggregation and fragmentation of the immunoglobulin.

REJECTION UNDER 35 USC § 112, second paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner alleges that the phrase "essentially free" is unclear because the metes and bounds of "essentially free" cannot be ascertained. Applicant respectfully traverses the rejection.

Applicant asserts that IgG4 "essentially free" of other IgG subtypes refers to an IgG4 preparation produced by the claimed manufacturing process. Applicant refers the Examiner to page 7, lines 26-27, of the specification wherein it is explained that the effluent collected after contact with the anionic and cationic exchange resin is mostly, if not entirely, IgG4. The specification defines such an IgG4 preparation as one that provides a high amount of blocking antibody, yet, does not lead to adverse reactions

when injected into a host (See, specification, page 5, lines 2-5). One of skill in the art would, therefore, understand that IgG4 essentially free of other IgG subtypes refers to, and can be defined by, the product of the method claimed in the present application. Furthermore, it is commonly understood that the term "essentially" means "fundamentally." Webster's Third New Int'l Dictionary 777 (1986). Similarly, "free of" means "without". Therefore "essentially free of other IgG subtypes" means "fundamentally without other IgG subtypes." See In re Marosi, 710, F.2d 799, 803, 218 USPQ 289, 291-292 (Fed. Cir. 1983) (interpreting "essentially free" to mean that a material is present only as an unavoidable impurity); and Glaxo Group Limited and Glaxo Wellcome, Inc., v. Ranbaxy Pharmaceuticals, Inc., 59 USPQ2d 1950 (Fed. Cir. 2001)(interpreting "essentially free from crystalline material" to mean "fundamentally without crystalline material"). Applicant therefore submits that one of skill in the art of purification and ion-exchange chromatography would understand the claim language "IgG4 essentially free of other IgG subtypes" to mean a preparation of IgG4 that is entirely IgG4 and does not contain IgG1, IgG2 or IgG3 subtypes, unless present in very small quantities as unavoidable impurities.

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner alleges that the phrase "immune donor" is unclear because the metes and bounds of the phrase "immune donor" cannot be ascertained. Applicant respectfully traverses the rejection.

Applicant refers the Examiner to the specification on page 1, lines 22-24, page 2, lines 3-6; page 3, lines 14-15; and page 4, lines 8-10. In these sections, the specification teaches that the blood plasma used in the claimed method comes from immune donors (page 3, lines 14-15) who are selected for high titers of specific antibodies (page 1, lines 22-24) and who already have hyper immune serum globulin (page 4, lines 8-10). Therefore, one of skill in the art would understand the term "immune donor," as recited in claim 5, to refer to a subject who has hyper immune serum

globulin and who has been selected for high titers of specific antibodies. One of skill in the art would know how to identify such an immune donor using standard methodologies.

In view of the foregoing remarks, Applicant respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 USC § 102(b)

Claim 1 stands rejected under 35 USC § 102(b) as allegedly being anticipated by Zolton *et al.*, U.S. Patent No. 4,597,966. The Examiner alleges that Zolton *et al.* anticipates the claimed invention because the immunoglobulin preparation of Zolton *et al.* would inherently comprise IgG4 and be essentially free of other subtypes. In response, Applicant respectfully traverses the rejection.

Zolton *et al.* does not expressly or inherently set forth the element that the plasma sample contact a *cation exchange resin*. Claim 1 of the present application expressly recites that the plasma contact an anion exchange resin followed by a *cation exchange resin*.

As the Examiner is well aware, for a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features or limitations of the presently claimed invention.

The rejection cites Zolton *et al.* as the basis for the § 102(b) rejection. Applicant respectfully submits that the Zolton reference does not disclose every element of the presently claimed invention and, thus, cannot form the basis for a § 102(b) rejection. Namely, the cited reference does not expressly or inherently disclose that the effluent obtained after applying the plasma to an anionic exchange resin be applied to a cationic exchange resin. As each and every element is not present in the prior art reference, Applicant respectfully requests that the Examiner withdraw the anticipation rejection.

FIRST REJECTION UNDER 35 USC § 103(a)

The Examiner has rejected claims 1 and 5 under 35 USC § 103(a) as allegedly being obvious over Zolton *et al.* in view of Cheung *et al.* (*Annals of Allergy*, Volume 50, 1983, p 155-160). The Examiner alleges on page 7 of the Office Action:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to obtain the sera used in the method of preparing a stabilized highly purified immunoglobulin preparation as taught by Zolton *et al.* from the immune donors (beekeepers) as taught by Cheung *et al.* because Cheung *et al.* teach that beekeepers that have frequent exposure to bee stings have few clinically significant reactions, have distinctly high honey bee venom (HBV) IgG levels and the association of high HBV IgG4 with beekeepers might suggest a biological role of HBV IgG4 in the protection against anaphylactic reactions or as a laboratory marker of protection.

In response, Applicant respectfully traverses the rejection.

M.P.E.P. § 2143 states the following:

> "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicant states that there is simply no motivation or suggestion provided in the cited references to prepare a IgG4 preparation, free of other IgG subtypes. As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Zolton teaches a method which results in a purified and stable IgG gamma globulin preparation containing all IgG subtypes, which preparation includes IgG1, IgG2, IgG3 and IgG4. The purpose of the Zolton method is to stabilize the immunoglobulin using histidine. Histidine acts as a substrate for proteases present in the serum. Therefore, Zolton teaches stabilized preparations of IgG, not methods of fractionating IgG into its various subtypes.

In stark contrast, the present method teaches a method of preparing IgG4, essentially free from other IgG subtypes, for injection into allergic individuals. The method employs an anion exchange resin followed by a cation exchange resin. Applicant asserts that there is simply no teaching or suggestion of fractionating the various IgG subtypes in Zolton.

The Examiner's attention is respectfully directed to the Declaration of Dr. William Pollack ("the Pollack Declaration") which accompanies this response. In

paragraph 6, Dr. Pollack declares that the manufacturing method described in Zolton *et al.* is significantly different from the one claimed in the present invention and therefore, results in a significantly *different* product from that described and claimed in the present application. Dr. Pollack declares in paragraph 6 that the Zolton method, unlike the presently claimed method, does not result in an immunoglobulin preparation comprising IgG4 that is essentially free of other IgG4 subtypes. Instead, Zolton's method results in a purified and stable IgG gamma globulin preparation containing all IgG subtypes, including IgG1, IgG2, IgG3 and IgG4. Dr. Pollack further declares that while the Zolton patent teaches methods of manufacturing stabilized preparations of IgG, the present application claims methods of fractionating IgG into its various subtypes. The purification system described in Zolton, therefore, could not result in pure IgG4 free of other subtypes as is presently claimed.

Further, Dr. Pollack declares in paragraph 7 that the Zolton purification method utilizes a QAE-Sephadex anionic resin whereas the purification method of the present invention utilizes two resins, an anionic resin. e.g., DEAE Sepharose, followed by a cation exchange resin, e.g., CM-Sepharose. Dr. Pollack confirms that this extra fractionation step provides the effluent that is purified IgG4 free of other subtypes. Dr. Pollack further confirms that prior to the advent of the present invention, the art of fractionation as it applies to purification of IgG into IgG4 was not known. According to Dr. Pollack, the present invention provides a facile method of manufacturing IgG4 immune globulin that is essentially free of other subtypes.

Zolton *et al.* teaches how to make a purified IgG preparation for injection into humans but does not teach how to fractionate IgG into its subtypes or even suggest that fractionation would be desirable. The secondary reference of Cheung *et al.* does not supply the teaching that is deficient in Zolton *et al.* Cheung *et al.* teaches a correlation between high IgG4 levels and beekeepers. This correlation, at most, indicates that there may be a role for IgG4 in the protection against anaphylactic reactions. Cheung *et al.* does not teach or suggest how to make purified IgG4 preparation or even that a purified IgG preparation would be more desirable than a IgG preparation, containing all of the

IgG subtypes including IgG4. As such, Applicant asserts that there is simply no teaching or suggestion of a method to purify IgG4 as is presently claimed. Therefore, Applicant respectfully request that the Examiner withdraw the rejection.

2. There is No Reasonable Expectation of Success

In addition, in view of the cited references, one of skill in the art would have no reasonable expectation of success that IgG4 can be purified from blood plasma. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

Applicant asserts that there is absolutely no teaching or suggestion in the cited art to modify the teaching therein to arrive at the presently claimed invention. Neither of the references, either alone or in combination, teach or suggest IgG4 fractionation. Furthermore, neither of the references use the same conditions, e.g., resin combination, pH, and conductivity, for purification. In view of the cited art, Applicant asserts that a skilled person, would have no expectation of successfully purifying IgG4 from IgG.

Methods of making IgG preparations have been known since the 1940's (Cohn *et al., J. Amer. Chem. Soc.* 68:459 (1946). However, a skilled person in view of Zolton or Cheung would have no expectation of successfully obtaining a IgG4 fraction free of other subtypes which is suitable for injection into humans. Applicant therefore respectfully requests that the Examiner withdraw the rejection.

3. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicant asserts that the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

Applicant claims a novel method of manufacturing purified IgG4. Under *In re Wilson supra, a prima facie* case of obviousness has not been established as each of the limitations of the claims is not taught or suggested in the cited art references. Zolton *et al.* does not teach or suggest a method for the fractionation of IgG4. Further, Zolton does not teach that the plasma contact an anion exchange resin followed by a *cation exchange resin*. Cheung *et al.* does not teach or suggest a method for the fractionation of IgG4.

As the prior art references do not teach every element of the claimed invention, Applicant respectfully requests that the Examiner withdrawal the rejection.

SECOND REJECTION UNDER 35 USC § 103(a)

Claims 1, 6, and 7 were rejected as allegedly being obvious over Zolton *et al.* in view of Sirna (U.S. Patent No. 5,908,827). The Examiner alleges on page 8 of the office action:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use a DEAE Sepharose and a CM-Sepharose in the method of preparing a highly stabilized purified immunoglobulin preparation as taught by Zolton *et al.* because Sirna demonstrates that the isolation of a raw fraction or protein during extraction and purification can be performed using a DEAE Sepharose and a CM Sepharose through ion exchange chromatography and high resolution chromatography.

In response, Applicant respectfully traverses the rejection.

Zolton has been discussed above. Sirna teaches the use of ion exchange chromatography and high resolution chromatography to extract purified polypeptide from human urine. Nothing in the Sirna reference suggests that a method of purifying polypeptide from *urine* can be used to purify immunoglobulins from *plasma*.

The Examiner's attention is respectfully directed to paragraph 11 of the Pollack Declaration. Dr. Pollack declares therein that one of skill in the art would not expect a purification system for the extraction of polypeptide from *human urine* to be

relevant for the purification of *blood plasma* and immunoglobulins. The reasons for this are numerous. The art of fractionation and ion exchange chromatography is unpredictable. Urine and blood plasma do not share a similar structure, size, ionic charge, or composition. Various resins, buffer, or pH levels that are suitable for the purification of polypeptides from urine are not suitable for the purification of immunoglobulins from plasma. Therefore, one of skill in the art of purification would not predict that a purification scheme effective for the purification of a specific protein from urine would be equally effective, or even marginally effective, for the purification of an immunoglobulin subtype from blood plasma. The chemical and structural differences of plasma and urine are simply too great. Sirna does not imply otherwise. Sirna prepares its purified protein by passing urine through eight separate resins. Additionally, in the Sirna patent, the urine is adsorped at low pH on kaloin and extracted with ammonia. In contrast, the method of the present invention uses only two resins and a plasma pH of 6.5. One of skill in the art would not be able to successfully purify IgG4 from blood plasma using Sirna's purification method.

Therefore, because Zolton *et al.* does not teach purification of IgG4 from IgG and Sirna does not teach purification methods relevant for IgG4 purification, the instant claims are in no way made obvious. As such, Applicant respectfully requests that the Examiner withdraw the second rejection under 35 U.S.C. 103.

THIRD REJECTION UNDER 35 USC § 103(a)

Claims 1,8, and 9 were rejected as obvious over Zolton *et al.* in view of Thomas (U.S. Patent No. 4,089,944). The Examiner states on page 10 of the office action:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the lactose as taught by Thomas in the method of preparing a highly stabilized purified immunoglobulin preparation as taught by Zolton *et al.* because Thomas teaches that the addition of monosaccharides enhance the rate of solubility in composition.

In response, Applicant respectfully traverses the rejection.

Zolton has been discussed above. Thomas teaches that the addition of monosaccharides enhances the rate of solubility in compositions. Thomas does not teach or suggest a purification method for IgG4, nor does Thomas suggest that IgG can be fractionated into its subtypes.

The Examiner's attention is respectfully directed to paragraph 12 of the Pollack Declaration. Dr. Pollack declares that Thomas's teaching on how to rapidly solubilize an anti-hemophilic factor composition in no way teaches or suggests how to make purified IgG4 preparations.

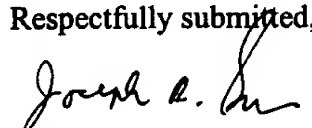
Therefore, because Thomas does not teach or suggest a method for the fractionation of IgG4 and Zolton *et al.* does not teach purification of IgG4 from IgG, the combined references do not teach or suggest a method for the fractionation of IgG4. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing remarks, Applicant believes that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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APPENDIX A

PENDING CLAIMS SUBJECT TO EXAMINATION

1. (Once Amended) A method of manufacturing IgG4 immune globulin that comprises the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

5. The method of claim 1, wherein said plasma is plasma obtained from an immune donor.

6. The method of claim 1, wherein said anion exchange resin is a DEAE Sepharose® resin.

7. The method of claim 1, wherein said cation exchange resin is a CM-Sepharose® resin.

8. The method of claim 1, further comprising the steps of:

(d) adding NaCl to a final concentration of 0.03 to 0.05 M NaCl;

(e) filtering the solution of step (d);

(f) centrifuging the filtrate of step (e);

(g) freezing the supernatant of step (f);

(h) thawing the frozen supernatant of step (g);

(i) adding a monosaccharide or disaccharide to the thawed supernatant of step (h) to a final osmolarity of between 0.22 to 0.35 OsM;

(j) filtering the solution of step (i);

(k) freezing the filtered solution of step (j);

(l) thawing the frozen solution of step (k); and

(m) lyophilizing the solution of step (l).

9. The method of claim 8, wherein said monosaccharide is lactose.